

Per-Fraction Positional and Dosimetric Performance of Prone Breast Tangential Radiotherapy Assessed with Daily Rapid Kilo-voltage Cone Beam Computed Tomography: Key Statistics, Predictors, and Recommendations

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Abstract

Background

This study investigates daily breast geometry and delivered dose to prone-positioned patients undergoing tangential whole breast radiation therapy (WBRT) on an O-ring linear accelerator with 6X flattening filter free mode (6X-FFF), planned with electronic compensation (ECOMP) method. Most practices rely on skin marks or daily planar image matching for prone breast WBRT. This system provides low dose daily CBCT, which was used to study daily robustness of delivered dose parameters for prone-positioned WBRT.

Methods

Eight patients treated with 16-fraction prone-breast WBRT were retrospectively studied. Planning CTs were deformed to daily CBCT to generate daily synthetic CTs, on which delivered dose distributions were calculated. A total of $8 \times 16 = 128$ synthetic CTs were generated. Consensus ASTRO definition was used to contour Breast PTV Eval for each daily deformed CT. Breast PTV Eval coverage (V90%) and hotspot (V105% and Dmax) were monitored daily to compare prescription dose with daily delivered dose. Various predictors including patient weight, breast width diameter (BWD), and Dice similarity coefficient (DSC) were fit into an analysis of covariance model predicting V90% and V105% deviation from prescribed ($\Delta V90\%$, $\Delta V105\%$). Statistical significance is indicated with asterisks (* for $p < 0.05$; ** for $p < 0.001$).

Results

Daily delivered Breast PTV Eval V90% was moderately smaller than prescribed (median $\Delta V90\% = -0.1\%^*$), while V105% was much larger (median $\Delta V105\% = +10.1\%^{**}$ or $+92.4\text{cc}^{**}$). Patient's weight loss correlated with significantly increased $\Delta V105\%$ ($+4.6\%$ / -1% weight, $R^2 = 0.4^{**}$) and moderately decreased $\Delta V90\%$ (-0.071% / -1% wt., $R^2 = 0.2^{**}$). Comprehensive ANCOVA models indicated three factors affect $\Delta V90\%$ and $\Delta V105\%$ the most: (1) BWD decrease ($-0.09\%^*$ and $+10\%^{**}$ / -1cm respectively), (2) PTV Eval volume decrease ($-0.4\%^{**}$ and $+9\%^{**}$ / -100cc), and for $\Delta V105\%$ only, (3) the extent of breast deformation ($+10\%^{**}$ / -0.01DSC). Breast PTV Eval volume also decreased with time ($-2.21\text{cc}/\text{fx}$), possibly indicating seroma resolution and increase in V105% over time.

Conclusions

Daily CBCT revealed key delivered dose parameters vary significantly for patients undergoing tangential prone breast WBRT planned with ECOMP using 6X-FFF. Patient weight, BWD, and breast shape deformation could be used to predict dosimetric variations from prescribed. Preliminary findings suggest an adaptive plan based on daily CBCT could reduce excessive dose to the breast.

Introduction

Breast cancer is diagnosed in about a quarter of a million women in the United States every year [1]. Lumpectomy with tangential-field, whole-breast radiotherapy (WBRT) is a standard treatment as part of breast conservation therapy (BCT) for early stage disease [2, 3]. Tangent WBRT can be delivered in either supine or prone position. Prone position may be optimal for patients with larger and more pendulous breasts for three reasons: (1) Reduced dose to heart and lungs [4], (2) respiratory motion of the chest walls and surgically inserted clip is reduced, consequently decreasing intra-fraction dosimetric variations [5], and (3) dose inhomogeneities in supine position raises the risk of late skin effects resulting in adverse cosmesis.

Daily image guidance is crucial in prone patient positioning, since immobilization devices alone cannot provide consistent day-to-day breast localization. Matching clips or bony / soft tissue anatomy with orthogonal electronic portal image devices (EPID) is a common standard for image guidance in prone WBRT. EPID positional accuracy is comparable to kV cone-beam CT (CBCT) guidance [6, 7]. Unlike EPID, however, CBCT can provide tomographic image from which 3-dimensional positional and dosimetric outcomes can be derived. Despite this advantage, busy clinics are discouraged from adopting daily CBCT because CBCT acquisition time may decrease throughput and increase imaging dose.

Halcyon™ v2.0 (Varian Medical Systems, Palo Alto, CA) is a commercially available 6MV flattening-filter-free O-ring linear accelerator that provides rapid daily kV CBCT image guidance for tangential WBRT. The O-ring design reduces the risk of collisions and enables higher gantry rotation speed for faster CBCT imaging, which demonstratively improved patient throughput in many clinical sites including whole breast [8, 9]. Compared to C-arm linacs, Halcyon v2.0 CBCT acquisition is faster (17–42 seconds versus 60 seconds), even after taking into account reconstruction duration for iterative CBCT, or iCBCT [10], which results in a better contrast-to-noise ratio.

One trade-off for higher patient throughput with Halcyon is the restriction to 6X-FFF beams, which results in a non-flat dose profile at depth. Electronic tissue compensation (ECOMP) planning technique [11] is a forward-planning technique that compensates for this non-flat profile to homogeneously treat an irregular surface (i.e. breast) using parallel opposed beams. In contrast, Field-in-field (FiF) is a more common planning technique for C-arm linacs. It has been previously demonstrated that FiF takes significantly longer on Halcyon (9 min FiF vs. 3–4 min ECOMP) owing to Halcyon's dual multi-leaf collimator (MLC) system.

It is unknown if ECOMP with FFF beam for prone WBRT meets dose coverage metrics (i.e. V90%) or hotspot metrics (i.e. V105%) on a per-fraction basis. American Society for Radiation Oncology (ASTRO) guidelines on whole breast RT state that V105% (volume of breast receiving 105% of prescription dose) should be minimized at all times [12], as V105% has been linked to adverse cosmesis [13]. ASTRO guidelines also state that V95% should cover the whole breast fully. The rapid CBCT capabilities of Halcyon v2.0 enables large-scale studies of dosimetric robustness, for example, by deforming planning

CT to daily CBCT. Such capabilities can guide adaptive radiotherapy decisions if needed should plans fail to meet the guidelines.

In this paper, we assess the daily positional and dosimetric quality of ECOMP with FFF beam for tangential-beam prone WBRT, using per-fraction CBCTs provided by Halcyon v2.0 during patient positioning to: (1) Assess daily dosimetric and positional robustness of our treatments using daily CBCTs in real patient cases, and (2) investigate what factors affect dose homogeneity most adversely. Assessment of these factors may possibly inform future adaptive RT decisions.

Methods

Overall Design of the Study

The purpose of this study is to evaluate daily positional and dosimetric accuracy of tangential-field prone WBRT, planned with ECOMP and treated with 6X-FFF beam on Halcyon™ version 2.0 (Varian Medical Systems, Palo Alto, CA). We seek to investigate what parameters affect target coverage and radiation hotspot the most, using Halcyon's rapid daily CBCT capabilities. This retrospective study was reviewed and approved by our Institutional Review Board.

Image acquisition was done as follows. Eight (8) prone breast patients receiving WBRT post-lumpectomy with hypofractionated schedule of 2.66 Gy x 16 fractions followed by 10 Gy boost were retroactively analyzed. CT simulation was performed after patients were immobilized on a commercially available prone breast board. A kV CBCT was taken before delivery of each fraction, as part of Halcyon v2.0 image-guided RT workflow. A total of 16 fx * 8 patients = 128 CBCT datasets were obtained. A synthetic daily CT was generated by deformably registering the planning simulation CT to each of the daily CBCT images using MIM Maestro® (MIM Software Inc., Cleveland, OH) version 6.6. CBCTs associated with boosts were excluded from daily evaluations.

The clinical treatment plans were generated using ECOMP technique (EZfluence™, Radformation, Inc, New York, NY) in Eclipse v15.6 (Varian Medical Systems, Palo Alto, CA), with dosimetric endpoints specified in Table 1. This plan was copied and recalculated on synthetic CT to obtain daily delivered dose distribution. BODY and Breast PTV_eval contours, as defined on Radiation Therapy Oncology Group (RTOG) trial 1005 [14] and RTOG census definitions [15] were created on each synthetic CT. The Breast PTV_eval contour was derived for each day of treatment, the process of which is clarified in the following subsections.

Dosimetric Endpoints Investigated

Most recent ASTRO guidelines on WBRT state that V105% should be minimized at all times, while some cite 200 cm³ as the recommended limit [12]. The tumor bed is to receive at least 95% of the prescription dose under ASTRO guidance. Similarly, RTOG1005 protocol stipulates (1) 95% of Breast PTV Eval shall

receive at least 95% of prescribed dose ($D_{95\%} > 95\%$, but $D_{90\%} > 90\%$ acceptable), and (2) maximum dose less than 115% of prescribed dose ($D_{max} < 115\%$, but 120% acceptable).

To investigate if delivered prone WBRT dose on Halcyon meets these guidelines on a per-fraction basis, three primary dose-volume metrics were measured at each fraction to assess PTV Eval coverage and hotspot: $V_{90\%}$, $D_{95\%}$, and $V_{105\%}$. Absolute values of $V_{95\%}$ [cc], $V_{100\%}$ [cc], and $V_{105\%}$ [cc], and global maximum dose (D_{max}) were obtained from the BODY contour. Predictive model for these dose-volume metrics were constructed, based on patient parameters including source-to-surface distance (SSD), couch shifts, residual breast position (defined below in Data Collection, Analysis, and Statistics section), and weight.

Patient Set-up and Initial Treatment Planning

Eight (8) patients were simulated head-first-prone on Siemens Sensation CT scanner (Siemens Healthineers, Erlangen, Germany) for initial treatment planning. Patients were immobilized with QFix® Prone Breast (Avondale, PA) boards and a vac-lok bag placed underneath the patient and with their arms up. Imaging isocenter was placed midline of the body, at the midpoint (sup-inf) of the breast tissue and anteriorly to the sternum.

WBRT was planned in Varian Eclipse v15.6. Physicians contoured Breast CTV based on consensus definitions [15]. Breast CTV was expanded 5 mm (excluding heart and not crossing the midline) and cropped anteriorly from the skin by 5 mm and posteriorly in front of the rib to obtain Breast PTV Eval. Treatment isocenter was shifted anteriorly to cover Breast PTV Eval. ECOMP technique was carried out by experienced dosimetrists. ECOMP is a forward-planning intensity-modulated radiation therapy (IMRT) technique using parallel opposed beams, where the goal is to deliver as homogenous dose as possible to an irregular surface. For breast, this is done by planning a uniform dose at mid-separation. Skin flash of 2 cm was added beyond the patient contour, and then the edited fluence maps were converted to leaf sequences for Halcyon dynamic MLC. Machine energy was fixed at 6X-FFF (6-MV with flattening filter free), with prescription dose of 266 cGy/fraction for all patients. Anisotropic analytical algorithm (AAA) version 15.6.03 was used for volumetric dose calculation. For photon dose optimization and irregular surface compensator generation, photon optimizer version 15.6.03 was used.

Dose-volume constraints for Breast PTV Eval in a whole breast treatment used at our institution are listed on Table 1. $D_{95\%}$ and $V_{90\%}$ measure the extent of dose coverage to the breast, while $V_{105\%}$ and D_{max} are measures of dose hotspots. For this study, a $< 200 \text{ cm}^3$ objective is additionally applied for the entire patient volume (BODY contour) as another suggested measure of homogeneity by ASTRO consensus but was not a constraint used clinically during planning. Study of normal organs, such as the lungs, hearts, and contralateral breast were omitted from this study.

Table 1
Dose-volume objectives for Breast PTV Eval

Breast PTV Eval	Evaluator	Variation Acceptable
DVH Objective		
D95%	$\geq 95\%$	$\geq 90\%$
V90%	$\geq 99\%$	$\geq 98\%$
V105%	$\leq 10\%$	$\leq 15\%$ / ≤ 200 cc to Breast tissue [12]
Dmax	$\leq 107\%$	$\leq 110\%$

Patient Treatment Workflow

For treatment on Halcyon v2.0 machines, patients were immobilized with identical QFix® Prone Breast boards and vac-loks used during simulation. Patients were scanned under Halcyon Breast protocol (125 kV, 491 projections at 10 mA and 10 ms, filtered back projection reconstruction) to obtain an on-board CBCT [10]. For 3D/3D matching, chest wall and ribs in the CBCT were aligned with those of the planning image, ensuring the breast in the CBCT is within the planning Breast PTV Eval contour. Online couch shift applied was saved in ARIA for all fractions. Patient body weight was acquired during the weekly on-treatment visit (OTV).

CT Deformation to Daily CBCT and Daily Treatment Planning

Figure 1A demonstrates the process to generate daily synthetic CTs using MIM Maestro v6.6. In the MIM console, planning CT was deformably registered to the CBCTs to generate synthetic daily CTs. Some synthetic CTs were discarded (2 in total) because of deformation failures stemming from limited CBCT field-of-view. A total of 126 synthetic CT images was extracted from MIM and imported back into Eclipse. Once imported, a copy of original RT plan was re-calculated on each of the synthetic daily CTs keeping all beam parameters intact, while taking into consideration the online CBCT-to-CT registration that was performed during daily treatment. Dose to synthetic daily CTs was calculated with the same AAA version as the original treatment plan.

Figure 1B demonstrates the contouring process on daily synthetic CTs for the treatment target, which is Breast PTV Eval contour. Original Breast PTV Eval contour (from the planning CT) were first copied into each daily synthetic CTs keeping the posterior edge shape and position relative to the chest wall the same as in the initial plan. The transferred PTV Eval was then modified using the same guidelines that was used to generate PTV Eval during the initial planning: a 5 mm subtraction from the breast tissue surface. The breast tissue surface was automatically determined by the Eclipse software in the contouring module for each of the synthetic CTs. Overall, this procedure ensures the PTV Eval structure generated on daily synthetic CT consistently represents the initial physician's intent on breast tissue being irradiated for each daily fraction.

We make a distinction between two categories of data: (1) planning data and (2) per-fraction / daily data. The former refers to the baseline parameters determined from planning CT and the planned dose. The latter refers to the treatment parameters determined from daily synthetic CTs and the *delivered* dose. The difference of daily data from planning data is denoted throughout this paper with an uppercase Greek delta (Δ). For example, $\Delta V105\% = \text{Daily } V105\% - \text{Planned } V105\%$.

Dosimetric endpoints of this study include the following. For Breast PTV Eval contour: V90% [%], D95% [%], and V105% [%]. For BODY contour: V95% [cc], V105% [cc], and global Dmax. Here, [%] means “percent of the contour volume” and [cc] means “absolute volume as centimeter cubed (cm^3).” Dose-volume histogram (DVH) was calculated using DVH Estimation Algorithm version 15.6.03.

Patient positioning and volumetric data relevant to this study include the following. For general daily positioning data: lateral (LAT), vertical (VRT), and longitudinal (LNG) couch shifts [cm]; source-to-surface distances (SSD) [cm] for each of the two parallel opposed beams; breast width diameter (BWD) derived from SSD, as illustrated on Fig. 1; and post-image-guidance Breast PTV Eval shift [cm] (after accounting for daily couch shifts), referred to as “residual shifts” in this paper, also illustrated on Fig. 1. SSD-derived breast width diameter (BWD) gives a rough estimate of the breast diameter, but also captures some set-up errors of the day resulting in SSD distortions. For example, if both lateral and medial beam SSD increases for the day, BWD decreases; this can be interpreted as either breast diameter decrease or improper breast set-up resulting in breast compression. The residual shift is how much the Breast PTV center-of-mass shifts compared to during CT simulation, after taking into account the couch shifts. For volumetric data: Dice similarity coefficient (DSC) for breast deformations and Breast PTV Eval volume [cc]. DSC measures the extent of overlap between two contours, in our case daily Breast PTV Eval (constructed as shown on Fig. 1B) and planning Breast PTV Eval. DSC is equal to unity when a perfect overlap is achieved, and is calculated as such:

$$\text{DSC} = \frac{2 (V_{\text{plan}} \cap V_{\text{daily}})}{V_{\text{plan}} \cup V_{\text{daily}}} \quad (1)$$

Other data collected in this study include machine data: collimator angles, gantry angles, and monitor units for each of the two parallel opposed beams. Patient weight data gathered during simulation and physician visits was spline-interpolated to estimate weight at every fraction.

All data collected were imported into MATLAB (Natick, MA) Version 2019a for data visualization and statistical analyses. Tables and histograms of predictor variables, dosimetric endpoints, and patient position information are presented with descriptive statistics. Non-parametric statistical tests (Wilcoxon signed-rank test) were used to compare daily delivered dose-volumes with dose-volume optimization

criteria (Table 1) and with planned dose-volumes. Pearson correlation coefficients among all variables studied are presented, with emphasis on statistical significance of the observed correlation.

Finally, robust parallel slopes model (a type of analysis of covariance or ANCOVA) was constructed [16] to fit Δ dosimetric endpoints using the following predictors: couch shifts, PTV breast residual shifts, Δ BWD, 1-DSC, Δ PTV Eval Volume, and Δ body weight. In this model, each patient is assigned an intercept but the slopes with respect to predictors are assumed to be equal, hence the term “parallel slopes.” The general fitted formula was:

$$Y = \beta_{0i} + \beta_1 X_1 + \dots + \beta_n X_n + \sigma \quad (2)$$

Here, Y is the Δ dosimetric endpoints (e.g. $\Delta V_{105\%}$), β_{0i} is the intercept for i^{th} patient, β_n is the slope for n^{th} predictor X_n , and σ is a normally distributed residual term. The individualized intercept β_{0i} for each patient attempts to compensate for patient-specific factors, such as the differences in optimized IMRT fields, machine parameters (gantry angles, monitor units), and other miscellaneous factors. A reasonable estimate of the slopes was made based on this model. Robustness of the model was improved with MATLAB’s default iterative robust least squares procedure using bi-square weights. This reduces effects of high-leverage data and outliers on the fit. Wald’s Test with the null hypothesis that $\beta_n = 0$ estimated statistical significance of each variable on the Δ dosimetric endpoints.

Significance was set at $\alpha = 0.05$ for most statistical analyses except for multiple tests, for which Benjamini-Hochberg procedure was applied to limit false discovery rate [17].

Results

Descriptive Statistics of Positional and Dosimetric Data

Table 2
Summary of daily volumetric and positional data

Variable	Value, Median (Range)	Mean \pm Stdev
Contour Volumes [cc]		
Breast PTV Vol	1095.20 (654.20-1343.70)	1040.21 \pm 218.26
Breast PTV Eval Vol	899.90 (540.70-1149.80)	852.00 \pm 196.96
Daily Couch Shift [cm]		
LAT	0.07 (-2.26-2.28)	0.05 \pm 0.92
LNG	-0.13 (-2.10-1.35)	-0.12 \pm 0.70
VRT	-0.14 (-2.20-1.93)	-0.13 \pm 0.63
MAG	1.08 (0.27-2.78)	1.19 \pm 0.57
PTV Eval Residual Shift [cm]		
LAT	-0.04 (-0.35-0.32)	-0.03 \pm 0.12
LNG	0.07 (-0.38-0.47)	0.05 \pm 0.19
VRT	0.06 (-0.32-0.43)	0.05 \pm 0.13
MAG	0.25 (0.05-0.49)	0.26 \pm 0.10
BODY V95% Residual Shift [cm]		
LAT	-0.01 (-0.60-0.46)	-0.03 \pm 0.22
LNG	-0.04 (-0.53-0.66)	-0.04 \pm 0.18
VRT	0.05 (-0.58-0.43)	0.03 \pm 0.16
MAG	0.27 (0.04-0.80)	0.30 \pm 0.15
Daily SSD [cm]		
Lateral Beam	85.45 (80.80-95.70)	86.24 \pm 3.91
Medial Beam	102.75 (94.70-104.80)	102.00 \pm 2.82
Lateral Beam Deviation from Planned	0.10 (-2.10-1.30)	0.08 \pm 0.58
Medial Beam Deviation from Planned	0.10 (-0.50-1.30)	0.18 \pm 0.42
Target Contour DSC		
Breast PTV Eval	0.93 (0.88-0.97)	0.93 \pm 0.02
BODY V95%	0.92 (0.88-0.96)	0.92 \pm 0.02
Loading [MathJax]/jax/output/CommonHTML/fonts/TeX/fontdata.js		

Variable	Value, Median (Range)	Mean \pm Stdev
Deviation from Planned / Simulation	-0.48 (-6.50-4.71)	-0.64 \pm 2.69
<i>Abbreviations:</i> cc = centimeter cubed (cm ³); PTV Eval = planning treatment volume for evaluation; LAT = lateral; VRT = vertical; LNG = longitudinal; MAG = magnitude; SSD = source-to-surface distance; DSC = dice similarity coefficient; Stdev = standard deviation.		

Table 2 summarizes descriptive statistics of planned and daily patient positioning and contour volume data, as well as difference from prescribed (Δ). Positional data include couch shifts and PTV residual shifts in three orthogonal directions (latitude, vertical, and longitude) and their magnitudes (directional shifts summed in quadrature), source-to-surface distance (SSD) for both parallel opposed (lateral and medial) beams, and DSC comparing planned versus daily target volumes. Daily couch shifts were within ± 2.5 cm in each of the three principal directions, with a mean magnitude of shift of 1.19 ± 0.57 cm. Couch shifts of 0.68 ± 0.40 cm were previously reported in the literature for 21 patients treated on C-arm linac [18]. Breast positioning was consistent, with target center of mass shifting only by 0.26 ± 0.10 cm or 0.30 ± 0.15 cm (PTV Eval and V95% contour center of mass, respectively). The DSC roughly captures breast deformation taking into account the daily couch shifts. At $DSC = 0.93 \pm 0.02$, the intersecting volume of daily and planned contours are 93% of their composite (union) volume and indicates a great set-up consistency. The $\Delta SSDs$ of lateral and medial beams were 0.08 ± 0.58 cm and 0.18 ± 0.42 cm from planned, respectively, with some $\Delta SSD > 1$ cm. Patient weights varied from -6.5% to $+4.7\%$ compared to during CT simulation.

Table 3 tabulates the six delivered dosimetric parameters for homogeneity (Breast PTV Eval V90%, D95%, V105%, BODY V95%, V105%, and global max dose) planned, daily delivered, and difference from prescribed / planned (Δ). Wilcoxon p-values indicate the probability that the median value meets the dose-volume objectives (set out on Table 1) for daily measurements or the probability that the median Δ is non-zero. While target coverage was stable, delivered dose had hotspots failing to meet objectives and varying from prescribed dose frequently. The median of daily PTV V105% [%] failed to meet the $< 10\%$ objective, at 13.15%. Median global max dose [%] was found to be $> 107\%$ at 108.85%, but BODY V105% [cc] was found to be < 200 cm³. Median values of all quantities were within the variation acceptable (see Table 1), but some were not within the treatment objective. Figure 2 shows histograms of daily delivered dosimetric outcomes and difference from prescribed (Δ). The number of treatments that meet the prescribed dosimetric endpoints (i.e. "pass") or has a small Δ (e.g. " $< 10\%$ ") are represented as a fraction out of all treatments (126) examined. The histograms corroborate that target coverage metrics were stable, but dose hotspot metrics were not. Dose objective $D95\% > 95\%$ was met 111 days out of 126 daily CTs examined, while $V90\% > 99\%$ was less frequently met at 74/126 (but 95/126 within variation acceptable, $V90\% > 95\%$). For difference from prescribed, $\Delta D95\%$ was $> -5\%$ for 123/126 days and $\Delta V90\%$ was $> -1\%$ for 111/126 days. BODY V90% deviated only slightly from planned, with a standard deviation of ± 51.0 cc with a bias of -16.3 cc. In contrast, PTV V105% $< 10\%$ was met only 50/126 days (68/126 within variation acceptable). Dmax was the most often not met, with only 21/126 days meeting the

Table 3
Summary of planned dosimetric parameters and day-to-day dosimetric results

Variable	Value, Median (Range)	Wilcoxon P-value
Planned Dosimetric Quantities		
Breast PTV Eval		
D95% [%]	97.73 (93.63–98.64)	-
V90% [%]	99.50 (95.50–100.00)	-
V105% [%]	0.10 (0.00-41.10)	-
BODY		
V90% [cc]	1174.64 (863.13-1698.72)	-
V105% [cc]	3.67 (0.00-390.63)	-
Global Max Dose [%]	105.59 (104.94-106.92)	-
Daily Dosimetric Quantities		
Breast PTV Eval		
D95% [%]	97.74 (82.56–99.51) [†]	N.S.
V90% [%]	99.30 (94.20–100.00) [†]	N.S.
V105% [%]	13.15 (0.00-72.50) [‡]	1.5×10^{-4}
BODY		
V90% [cc]	1107.75 (831.38-1905.60)	-
V105% [cc]	130.45 (0.00-640.39) ^{†°}	N.S.
Global Max Dose [%]	108.85 (104.92-115.08) [‡]	4.4×10^{-16}
Difference from Prescribed (Δ)		
Breast PTV Eval		
Δ D95% [%]	-0.04 (-11.07-1.78)	N.S.
Δ V90% [%]	-0.10 (-1.70-0.20) [*]	6.1×10^{-11}
Δ V105% [%]	+ 10.10 (-15.40-72.50) [*]	6.3×10^{-16}
BODY		
Δ V90% [cc]	-18.07 (-155.14-206.87) [*]	3.4×10^{-3}

Variable	Value, Median (Range)	Wilcoxon P-value
$\Delta V105\%$ [cc]	+ 92.40 (-120.24-596.96)*	9.4×10^{-18}
Δ Global Max Dose [%]	+ 2.43 (-3.02-6.59)*	6.7×10^{-17}
<p><i>Abbreviations:</i> cc = centimeter cubed (cm³); PTV Eval = planning treatment volume for evaluation; N.S. = not significant</p> <p>* Significantly different from planned (two-tailed Wilcoxon).</p> <p>† Median value meets objective (one-tailed Wilcoxon).</p> <p>‡ Median significantly lower / higher than objective (one-tailed Wilcoxon).</p> <p>° BODY V105% does not have an objective, but ASTRO recommends < 200 cm³ to breast.</p>		

Dosimetric Performance per Patient

Figure 3 presents PTV V90%, D95%, V105%, BODY V95%, V105%, and global Dmax over the course of 16 fractions as a boxplot. Most metrics deviated from their planned values (indicated as a blue X) with statistical significance indicated within the parenthesis. Measures of coverage (V90%, V95%, and D95%) sometimes decreased during treatment versus planned ($\Delta < 0$). Measures of dose hotspots (V105% and Dmax) generally increased during treatment versus planned ($\Delta > 0$). Some patients, such as patients 2 and 5, experienced both decrease in coverage and increase in dose hotspots.

Correlation of Variables and Multiple Linear Regression

Figure 4 depicts Pearson correlation matrix among 21 variables studied in this paper, with only statistically significant Pearson coefficients ($p > 0.0177$) displayed after multiple testing corrections. Negative correlations are colored blue and positive correlations are colored red. The first variable (column or row) represent change with respect to time (fraction number). The next 8 variables represent daily couch shifts, followed by residual shift of the breast center-of-mass. The next 4 variables represent daily patient geometry: dice coefficients (deformation) of Breast PTV Eval contours, SSD-derived BWD, weight, and Breast PTV Eval volume. Remaining 6 parameters are the study endpoints: PTV and BODY dose-volume data. The uppercase Greek delta (Δ) denotes change with respect to planned or simulated (for example, Δ Body Weight [%] means change in patient body weight compared to during simulation).

The first column (or row) shows trends of each variable with respect to time. The magnitude of Breast PTV Eval residual shift increased with time ($r = + 0.3$), while volumes of PTV Eval and V95% decreased with each fraction ($r = -0.2$ and $- 0.3$, respectively). Breast volume decreased on average $- 2.21$ and $- 3.05$ cc per fraction for Breast PTV Eval and Body V95% respectively ($p = 0.026$ and 0.0018 , Robust linear regression). Daily couch shifts, where LAT is positive towards patient right (in prone position), LNG is positive towards patient head, and VRT is positive towards patient posterior (again, in prone position),

shifts correlated with residual shifts. Interestingly,

LNG couch shift correlated with PTV Eval Volume ($r = -0.3$). Breast deformation (DSC), body weight, and BWD correlated heavily with each other, as well as with dosimetric endpoints. Breast PTV Eval DSC correlated strongly with body weight ($r = +0.6$), suggesting that breast deformation increases with decreasing body weight. Body weight positively correlated with BWD, albeit weakly ($r = +0.3$).

Correlation of body weight with DSC, BWD, and dosimetric endpoints are plotted in Fig. 5. While some patients lost weight, some maintained weight throughout the course of treatment. Weight loss decreased DSC (or increased breast deformation) and moderately decreased BWD. The change in body weight from simulation (Δ) correlated positively with metrics of dose coverage like PTV $\Delta V90\%$ ($r = +0.4$, slope of 0.071% per weight %) and negatively with metrics of hotspot like $\Delta V105\%$ ($r = -0.6$, slope of -4.6% per weight %).

The results of comprehensive robust multiple linear regression fit are presented on Additional files 1 and 2. Additional file 1 tabulates the slopes (β_n) estimated for each variable. Additional file 2 tabulates the estimated intercepts (β_{0i}) for i^{th} patient and the overall adjusted R^2 for the model. Each model predicts Δ dose-volume metric. $\Delta D95\%$ was excluded due to lack of daily plans providing large variations in $D95\%$ which resulted in a poor fit (low adjusted $R^2 = 0.4$).

Discussion

Overall, the metrics of dose coverage such as PTV $D95\%$ [%], PTV $V90\%$ [%], and BODY $V95\%$ [cc] are both typically within the variation acceptable and robust on a day-to-day basis. Evidence supporting both claims can be most clearly seen in Fig. 2. On the other hand, metrics of radiation hotspot such as $V105\%$ and global hotspot (D_{max}) met the prescribed objectives less often, as seen on Fig. 3. In some patients (2 and 5) the BODY $V105\%$ was consistently > 200 cc on a daily basis even when the planned dose met this constraint, while the other 6 patients in this study consistently met the criteria.

Patient body characteristics such as weight, SSD-derived BWD, and breast volume may explain elevated $V105\%$ and D_{max} in some of these patients. For example, on Fig. 5, intra-patient ΔD_{max} increased by 0.53% and PTV $\Delta V105\%$ increased by 4.6% for every 1% weight loss from CT simulation (reminder that Δ signifies difference from prescribed). Patient 2 lost $\sim 4\%$ of her weight since CT simulation even before treatment began and 2% more during the course of the treatment. It is possible that dose delivered to patient 2 failed to meet dose constraints due to the significant weight loss.

Weight loss likely correlates with $\Delta V105\%$ and ΔD_{max} because it decreases breast deformation (DSC) and BWD. In our comprehensive parallel slopes model (Additional file 1), reduced DSC and BWD resulted in increased $\Delta V105\%$ and ΔD_{max} . Since weight loss decreases BWD and DSC (Fig. 4 and Fig. 5B), weight loss should increase $\Delta V105\%$ and ΔD_{max} according to the parallel slopes model. Interestingly, weight was not a significant predictor of $\Delta V105\%$ and ΔD_{max} when both BWD and DSC was present. It is possible that including these two variables in the model effectively cancel out the influence of weight loss on $\Delta V105\%$ and ΔD_{max} .

DSC and BWD reduction from weight loss were not the sole cause of $\Delta V_{105\%}$ and ΔD_{max} increase. In our model, PTV eval volume also significantly influenced intra-patient variability in $\Delta V_{105\%}$ and ΔD_{max} . Surprisingly, weight did not correlate with PTV eval volume (Fig. 4). This is interesting since breast volume is expected to decrease with weight loss. It is possible that post-lumpectomy seroma resolution is decoupling breast volume from weight loss. Indeed, PTV eval volume as a whole was also observed to decrease with time ($r = -0.2$) in Fig. 4, suggesting gradual seroma resolution over the treatment course.

In our model for dose coverage metric PTV $\Delta V_{90\%}$, BWD, weight, and PTV Eval volume influences dose coverage along with some positional shifts (namely: vertical couch shift, longitudinal residual shift, and magnitude of residual shift). It is unclear why these specific couch and residual shifts decrease PTV $\Delta V_{90\%}$. It is possible that negative vertical couch movements (i.e. couch moves down) increase PTV $\Delta V_{90\%}$ since that encourages more of the PTV Eval Breast to be within the field. It is also possible that residual shifts decrease PTV $\Delta V_{90\%}$, because any post-couch-shift residual movement of the breast will knock the breast out of the confines of the parallel-opposed field. Nevertheless, the slopes of these predictors with respect to PTV $\Delta V_{90\%}$ are quite small compared to PTV $\Delta V_{105\%}$, again corroborating that $\Delta V_{90\%}$ is robust.

A general guideline to reduce hotspots can be established based on the conclusions from parallel slopes model to ensure dose hotspot is limited and dose coverage is maximized. First, patient's weight and breast volume should be monitored closely for any extreme changes. Second, if patient weight loss or breast volume changes is over a certain threshold, BWD and breast volume should be re-examined during daily CBCT. A re-plan should be considered if BWD or breast volume changed significantly and would result in excessive hotspots or a significant loss in dose coverage.

The following are preliminary recommendations based on the estimated parameters from the model established on Additional files 1 and 2 and on the dose-volume objectives laid out on Table 1 during the course of the treatment:

- During CT simulation and planning, measure breast width diameter and extract breast volume from Breast PTV (not Breast PTV Eval).
- If a patient lost weight by $> 3\%$ compared to during simulation, re-measure breast width diameter and breast PTV volume of the patient in prone position henceforth, even if the patient's weight normalizes.
- If a two-day average of either patient's breast width diameter or breast volume deviates more than 1.5 cm or 200 cc compared to during CT simulation, respectively, consider a re-plan for the subsequent fractions.

The goal of the recommendations above is to limit per-fraction PTV $\Delta V_{105\%}$ (change from planned) to $< + 15\%$, without significantly affecting clinical workflow and treatment time. Note that, because BWD is derived from SSD, it is subject to set-up errors. The two-day average helps smooth out the daily variations due to set-up errors. Weight is a metric that is easy to measure during weekly on-treatment visits and can

be obtained more frequently easily. Since 1% weight loss results in 4.6% increase in PTV $\Delta V_{105\%}$, 3.3% weight loss corresponds to PTV $\Delta V_{105\%}$ of + 15% (rounded down to 3%). Additional file 1 shows that PTV $V_{105\%}$ increases by 10.1% (BODY $V_{105\%}$ by 83.2 cc) for every 1 cm decrease in BWD, all other variables being equal. PTV $V_{105\%}$ increases by + 8.79% (BODY $V_{105\%}$ by + 86.2 cc) for every 100 cc decrease in breast volume. That meant a 200 cc increase in Breast PTV (not breast PTV eval) leads to about + 15% increase in PTV $V_{105\%}$, taking into account the PTV Eval to PTV volume ratio of ~ 1.21 . Note that, if weight cannot be measured regularly, one can skip measuring the weight and monitor the two-day averages of breast width diameter (as defined in Fig. 2) and volume daily.

There are several limitations with the model despite the high adjusted R^2 reported (0.94 for $V_{105\%}$ and 0.84 for $V_{90\%}$). The β_{0i} intercept estimates (Additional file 2) show inter-patient biases are quite significant for $V_{105\%}$ and Dmax that cannot be fully explained by the β_n slope components of the regression. It is expected that all slopes should be zero if there were no patient-to-patient biases that predisposes one patient to receive higher or lower dose. There may be second order effects, interaction effects (i.e. variable slopes per patient rather than a single slope), or simply effects from personalized optimized IMRT fields that explain the non-zero intercepts. Another explanation could be that dose-volume metrics like $V_{90\%}$ and $V_{105\%}$ are inherently non-linear. Whatever the case may be, slopes on Additional file 1 should only be used to estimate intra-patient variations (i.e. fraction to fraction), never inter-patient variations.

Another limitation is that the model is statistically low-powered ($n = 126$, but only 8 patients) and fails to explain a few outlier or non-linear behaviors. In addition, despite the use of robust methods, our results may have been affected by patient 2, who experienced disproportionately severe weight loss than other patients in the trial. There were outlier behaviors the model did not predict as well, such as significant under-dosing (i.e. low PTV $V_{90\%}$) close to the chest wall for some fractions. For the two cases where BODY $V_{105\%}$ [cc] was exceptionally high, there was an unexpected high-dose area near the arm outside of PTV for one patient (P4, fraction 7) and a significantly decreased breast size for another (P5, fraction 15).

Conclusion

We examined and modeled the daily behavior of dose homogeneity for tangential field prone-positioned WBRT, using daily Halcyon v2.0 kV CBCT. The goal was to assess day-to-day robustness of electronic tissue compensation (ECOMP) technique with 6X-FFF, a modality that is unique to Halcyon. While metrics of dose coverage such as $V_{90\%}$ was often met, metrics of dose hotspot such as $V_{105\%}$ and Dmax routinely exceeded specified dose constraints on a per-fraction basis for select patients. Data suggests inter-patient differences in dose hotspot could come from patient body characteristics, such as weight, breast volume, and SSD-derived breast width diameter (BWD). In the comprehensive model, three factors explained most intra-patient variations in $V_{105\%}$ and Dmax: breast volume, BWD, and breast deformation compared to planned. For some patients, severe weight loss affected breast width diameter and breast

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losses independently of weight, possibly due to seroma resolution, that significantly increased V105% and moderately increased Dmax. Data suggests that some patients vulnerable to extreme weight loss or breast volume changes from seroma resolution may benefit from re-planning.

Abbreviations

WBRT

Whole breast radiation therapy

6X-FFF

6MV flattening filter free

ECOMP

Electronic compensation

PTV

Planning Treatment Volume

BWD

Breast width diameter

DSC

Dice similarity coefficient

BCT

Breast conservation therapy

EPID

Electronic portal image devices

FiF

Field-in-field

MLC

Multi-leaf collimator

Radiation Therapy Oncology Group

cc

Centimeter cubed (cm³)

SSD

Source-to-surface distance

CTV

Clinical target volume

AAA

Anisotropic analytical algorithm

DVH

Dose-volume histogram

LAT

Lateral

VRT

Vertical

LNG

Longitudinal

MAG

Magnitude

N.S.

Not significant

ANCOVA

Analysis of covariance

Declarations

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Ethics approval and consent to participate

This study protocol was reviewed and approved by the institutional review board of University of Pennsylvania (Reference No.: 831888).

Consent for publication

All data were stored in the hospital database and extracted for research. The participants' informed consent requirement was waived due to the retrospective nature of this study.

Availability of data and materials

The datasets used during the current study are available from the corresponding author on reasonable request.

Competing interests

NT is on an advisory board for Varian Medical Systems. LD owns a patent with Varian Medical Systems unrelated to this work. JM is a consultant for Varian Medical Systems. TL has received research grants from Varian Medical Systems unrelated to this work.

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Contributions

SY and TL conceived the study; GF, SA, CK, NT, KT, WZ, and TL collected the clinical data; SY analyzed and interpreted the data; SY wrote the manuscript; GF, LD, SA, EH, CK, JM, NT, KT, WZ, and TL provided critical review and revision of the manuscript; All authors reviewed the results and approved the final version of the manuscript.

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Figures

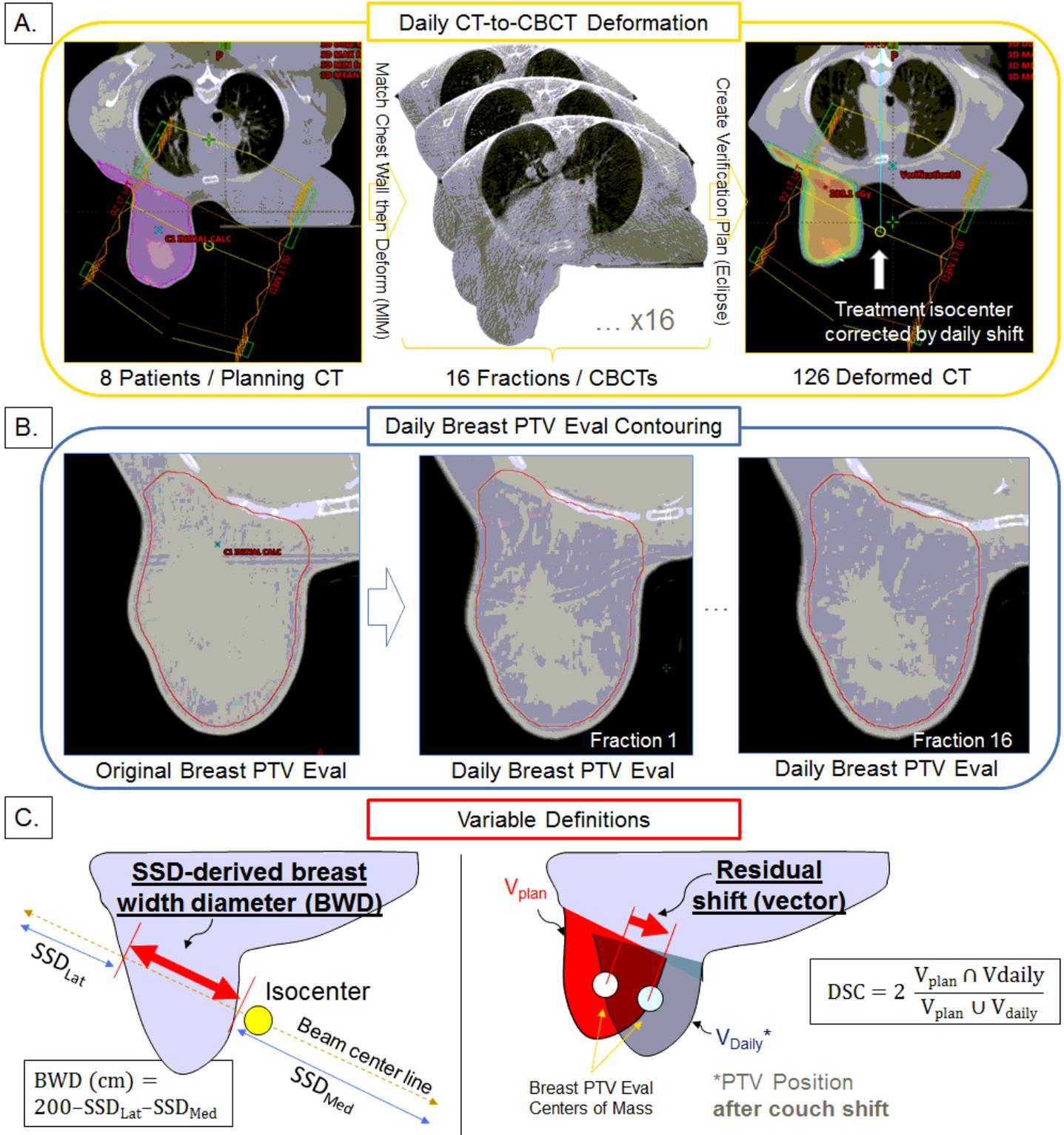
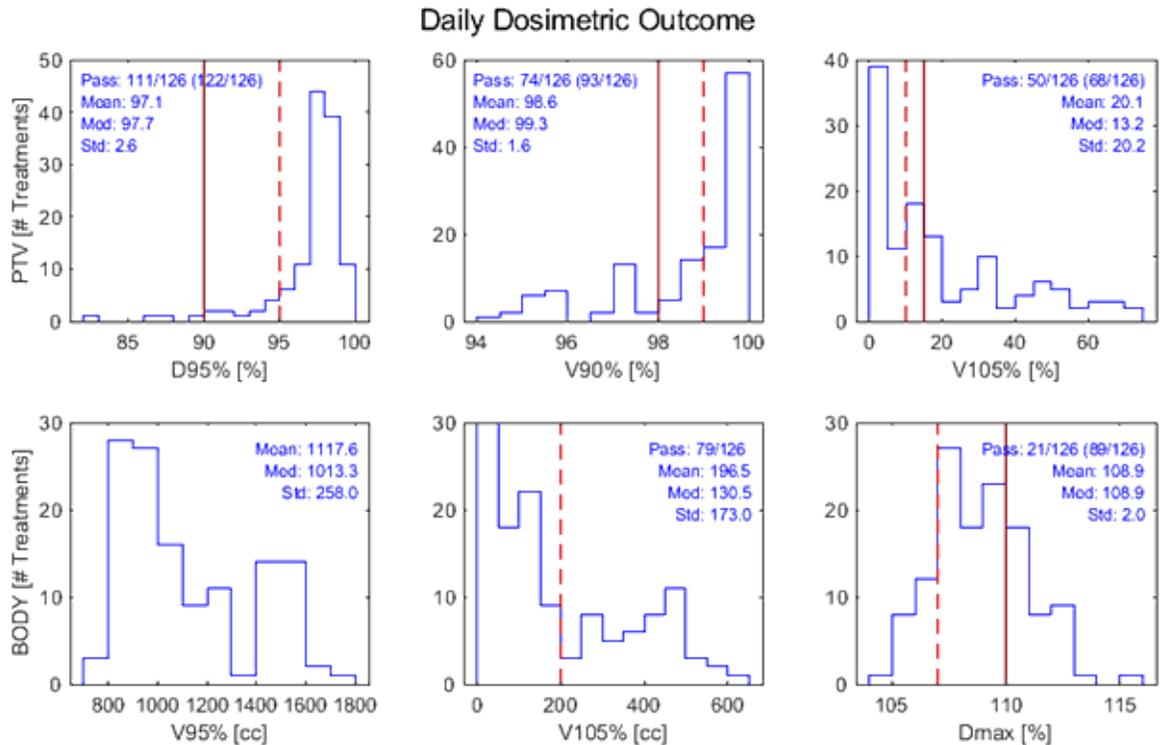


Illustration of daily synthetic CT generation and Breast PTV Eval contouring methods, as well as visual representation of variables used in predictive modeling. A. Planning CT for 8 patients were deformed to each of 16 daily CBCTs taken by Halcyon v2.0. A total of 126 deformed CTs were generated. The daily shift from matching CBCT-CT was applied to copied plan isocenter to correct for daily couch shifts. B. Generated Daily Breast PTV Eval mimicked the original contour as closely as possible, including a 5mm subtraction from the skin surface. C. Some predictive variables used in this paper are defined here. SSD-derived breast width diameter (BWD) is calculated from source-to-surface distances (SSD) of lateral and medial beams, giving an estimate of patient's breast diameter as well as any set-up errors resulting in distorted SSDs. Residual shift vector was derived from comparing centers of mass of planned breast PTV eval volume to that of daily volume, adjusted for couch shift. Dice similarity coefficient (DSC) was calculated from this same setup using the intersection and union of PTV volumes.

A.



B.

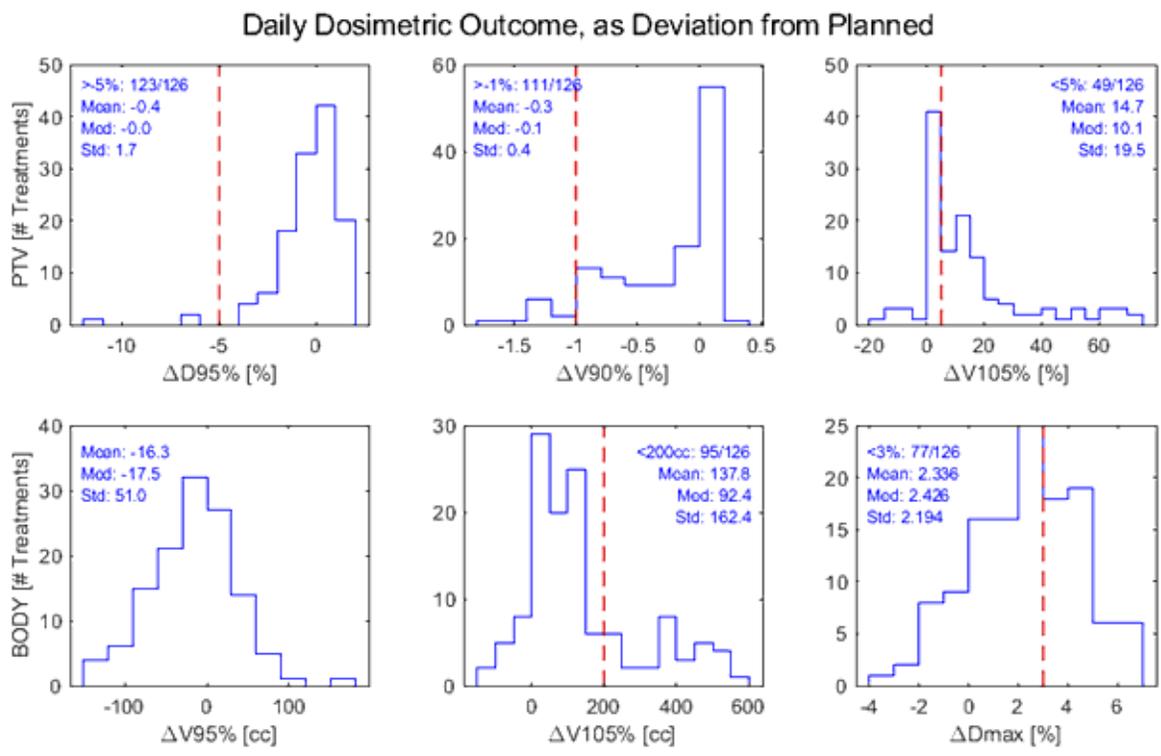


Figure 2

Histograms of daily dosimetric outcome based on Breast PTV Eval and BODY contours. Red vertical lines represent dose-volume constraints as defined on Table 1 (dashed: treatment objectives, solid: variation acceptable). Abbreviations: Med = median; Std = Standard deviation. A. Top row: dosimetric endpoints for the Breast PTV Eval contour. Bottom row: for BODY contour. Number of treatments that meet the dose-

fraction out of 126, in the following format

'N/126 (M/126)' where N = # meeting objectives and M = # within the variation acceptable. B. Corresponding histograms of daily dosimetric outcome, represented as difference from what was originally planned for the treatment courses. Number of treatments that do not deviate significantly from planned (N) are represented in format 'N/126', where "significant deviation" means "minimum deviation that would cause a plan meeting all dosimetric endpoints to extend beyond variation acceptable.

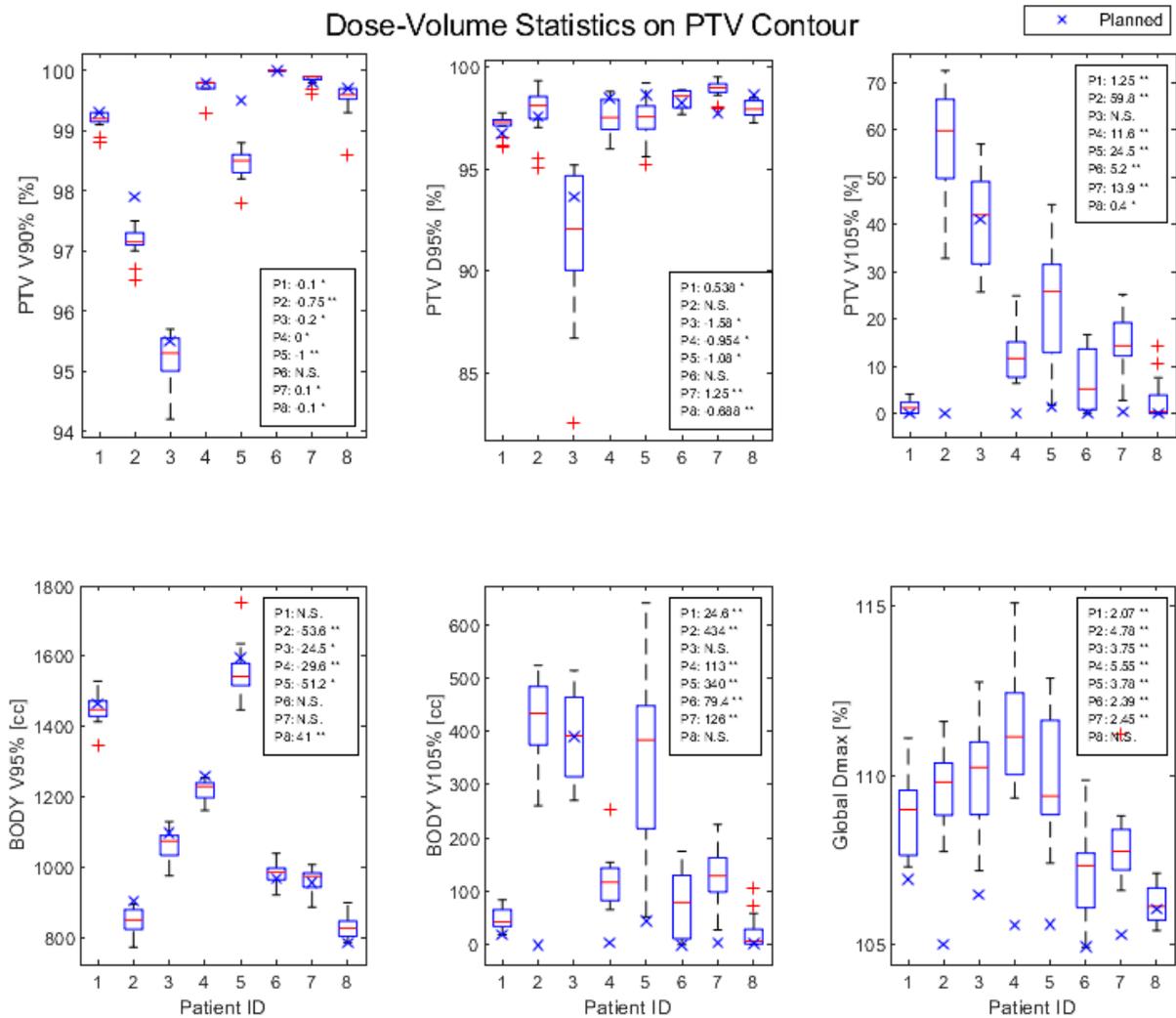


Figure 3

Boxplot of dose-volume quantities over the course of 16 fractions. Blue X represents planned quantities for each patient. Red + represents outlier fractions over the course of 16 fractions. Inset box: Median difference between planned quantities and daily quantities, with associated p-value (Wilcoxon signed-rank test) for each patient P1-P8. Statistical abbreviations: N.S. = not significant ($p > 0.05$); * = significant ($0.001 < p < 0.05$); ** = very significant ($p < 0.001$).

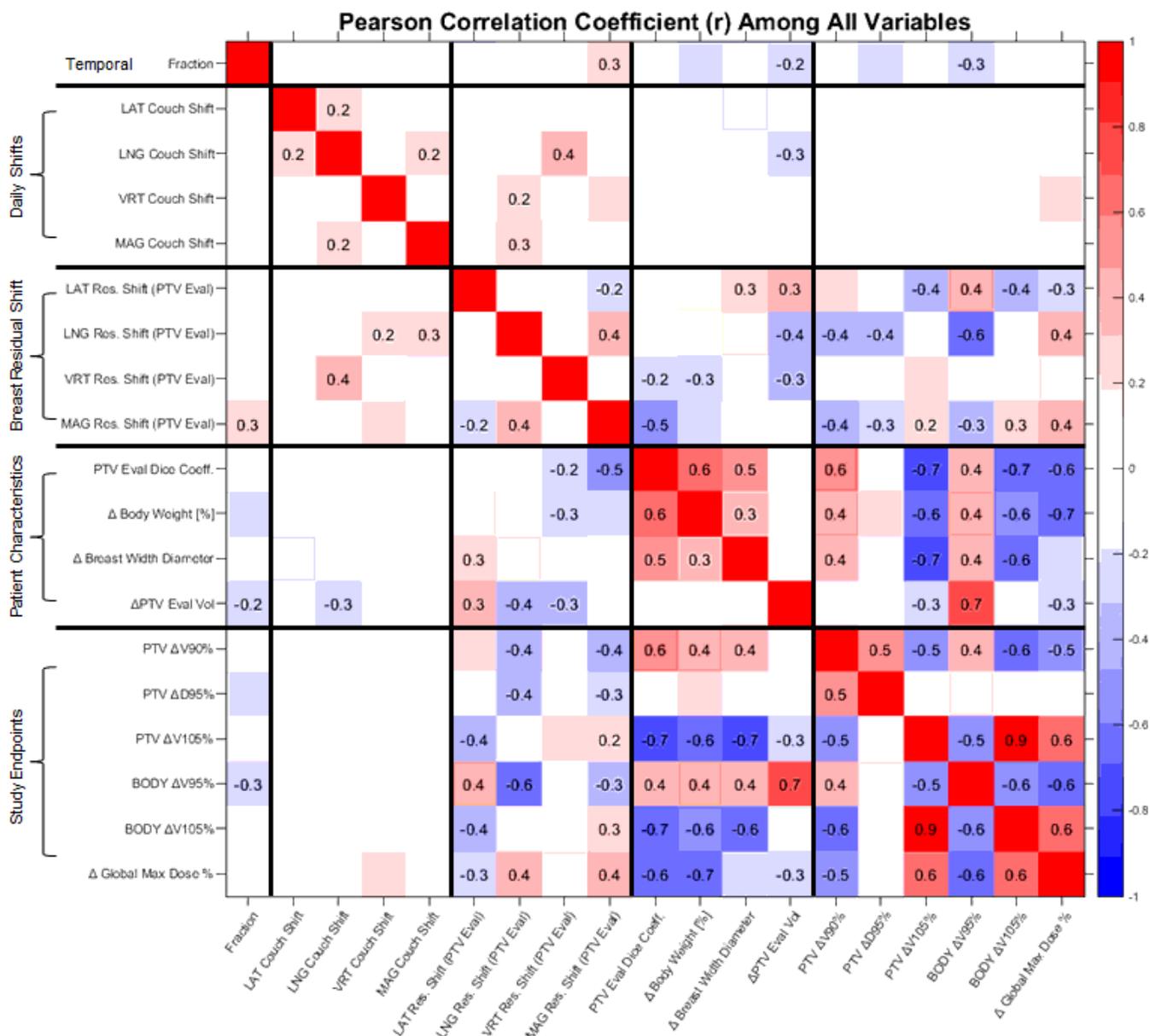


Figure 4

Pearson correlation coefficients among all data gathered. Negative correlations are represented by blue color. Positive correlations are represented by red color. Pearson correlation coefficient (r) is shown only when statistically significant (significance set to $\alpha = 0.0177$ via Benjamini-Hochberg procedure for multiple testing).

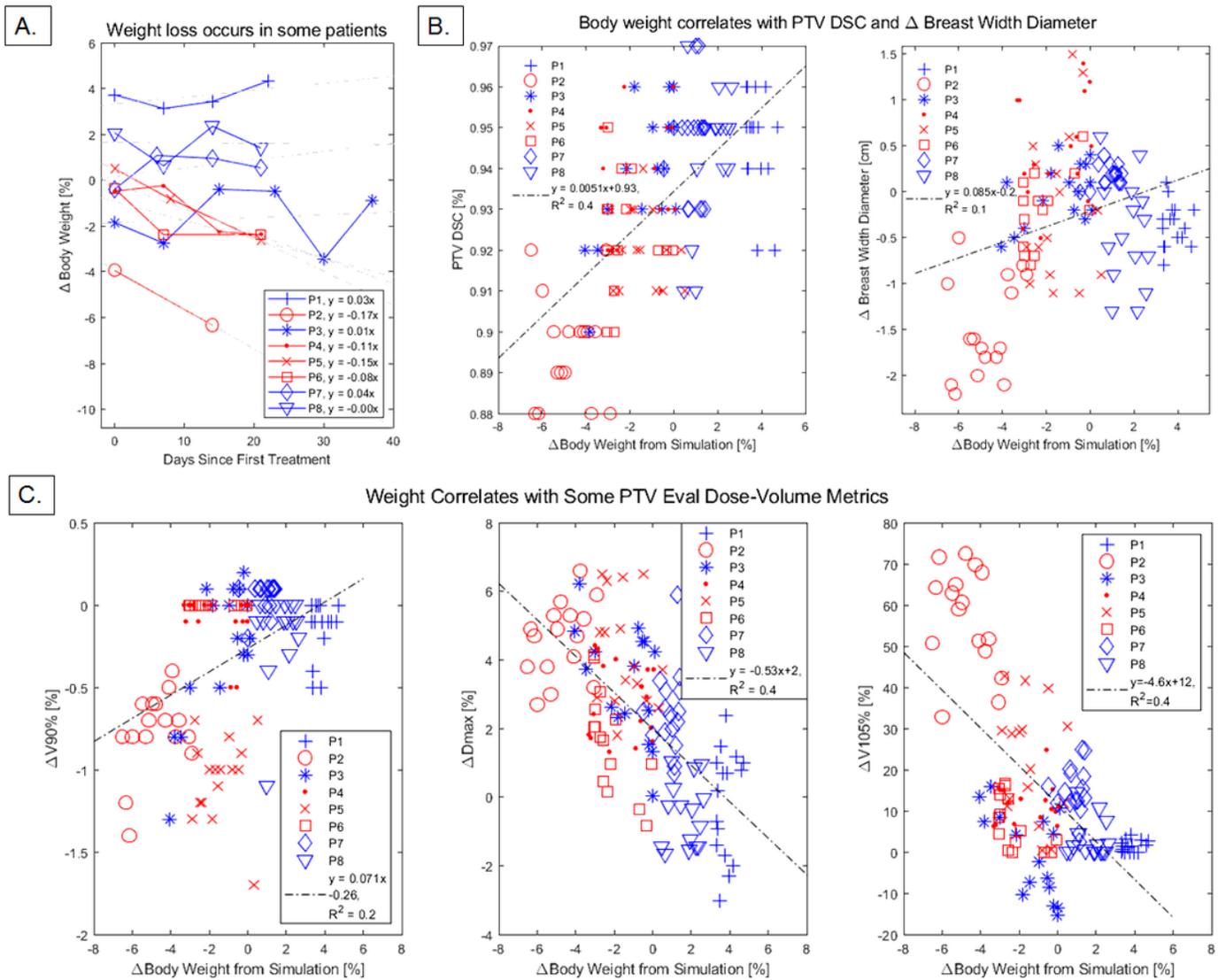


Figure 5

Body weight correlates with DSC, BWD, and PTV dose homogeneity and hotspot metrics. Data from patients who consistently lost weight over the course of the treatment are denoted in red (P2, P4, P5, and P6), while others are denoted blue. Linear fits (dotted lines) with equations and regression coefficient are also shown. A. Some patients were susceptible to weight loss, with one patient (P2) losing 4% body weight from simulation even before treatment began. B. DSC and BWD correlated to body weight. C. Breast PTV Eval Δ V90%, Δ Dmax, and Δ V105% (Δ = change from planned) correlates well with Δ body weight. Weight loss correlated to decreased PTV V90%, increased Dmax, and increased V105%, highlighting its crucial role in target coverage and reduction of hotspot.

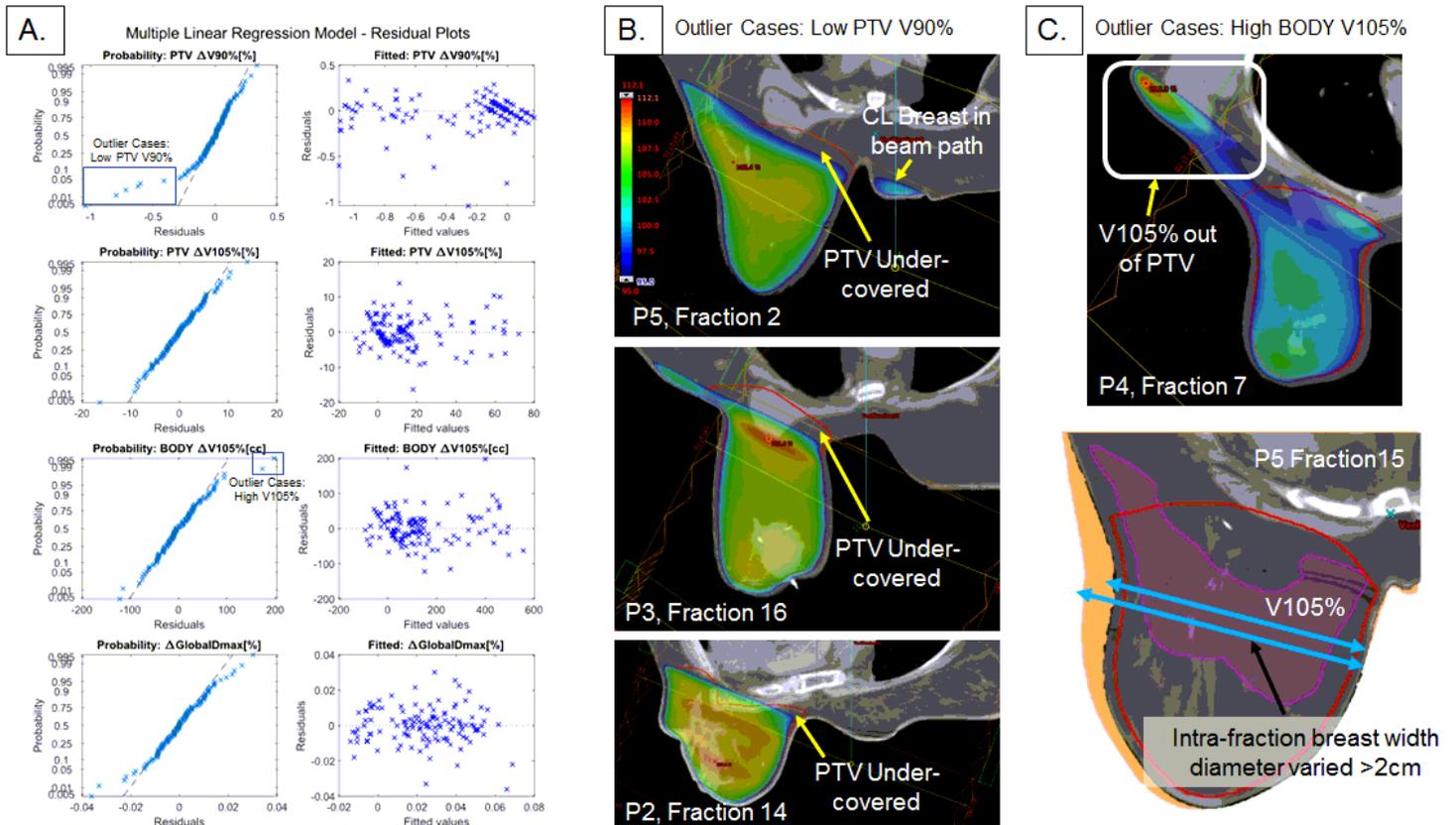


Figure 6

Robust parallel slopes model residual (σ) plots and examination of model outliers. A. Residual normal probability plot and residual versus fitted values plot. Residuals did not necessarily follow a normal distribution, for example for PTV $\Delta V90\%$ [%] and BODY $\Delta V105\%$ [cc]. Residuals were homoscedastic. B. Representative outlier cases where PTV $\Delta V95\%$ [%] was exceptionally low. Dose map ranges from 95% of prescription dose (blue) to respective maximum dose (red). PTV under-coverage occurred mostly at the chest wall. The beams were also very close to the contralateral (CL) breast and in one of the cases (patient 5, fraction 2) were irradiated outright above 95% of the prescription dose. C. Representative outlier cases where BODY $\Delta V105\%$ was exceptionally high. In the top case (patient 4, fraction 7), an area outside of the PTV contour was discovered that unexpectedly increased the BODY $\Delta V105\%$. In the bottom case (patient 5, fraction 15), the breast was highly deformed compared to the previous fraction (orange).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile2.xlsx](#)
- [Additionalfile1.xlsx](#)